UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/822,033	03/24/1997	WAYNE A. MARASCO	43471-FWC	5884

7590 05/12/2004

Ronald I. Eisenstein
NIXON PEABODY LLP
101 Federal Street
Boston, MA 02110

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/822,033	MARASCO ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Petition decision

The petition made under 37 CFR 1.181 filed February 19, 2003, requesting withdrawal of the finality of the office action has been **Approved** (see paper number 46 filed March 19, 2003). Accordingly, the finality of the previous office action has been withdrawn.

DETAILED ACTION

This application is a file wrapper continuation of 08/199, 070, filed February 22, 1994.

Claims 1, 3-16 are pending and currently under examination.

Response to Amendment

The declaration of Dr. Wayne A Marasco filed on June 11, 2003 has been received and entered. The contents of the declaration will be discussed in detail below as it pertains to the rejection of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 7-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* for the reasons below and as set forth in the previous office action.

Applicants argue that the combined references of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* do not anticipate the claimed invention because they in no way suggest that a recombinant fusion protein would deliver a nucleic acid more precisely that a fusion protein generated by chemical means rather than recombinant means (see Applicants amendment filed June 13, 2003, middle of page 5). More specifically, Applicants argue that nothing in the art supports that use of a recombinant protein would provide greater specificity than a protein made by chemical conjugation as exemplified in a post filing reference by Li *et al.* (2001)(see declaration sections 17-18 and Applicants' amendment bridging pages 7-8). The declaration of Dr. Marasco discusses in detail the evidence provided in figures 6C and 7B in the Li *et al.* reference noting an 8 to 10 fold increase higher expression in cells which express the ErbB2 cell surface receptor versus cells which do not express ErbB2 receptor that would not have been expected based on the teachings of Beug *et al.*, Chaudhary *et al.* or Wu *et al.* Applicants detail the teachings of each Beug *et al.*, Chaudhary *et al.* and Wu *et al.* noting the difference between the claimed invention and the deficiencies of each of the cited references. With respect to Beug *et al.* Applicants argue that the instant invention does not have the flexibility of including different/greater ratios of nucleic acid versus targeting moiety (bottom of page 6). Further, the

teaching of Beug *et al.* of use of an antibody is only in passing, and combined with the teaching of Wu *et al.* who primarily teach the use of "ligands" one would not conclude that an antibody is an effective means to target a fusion protein (starting at the bottom of page 5 to page 6). With respect to Chaudhary *et al.* Applicants argue that one would not use the teaching to deliver a nucleic acid because the teaching of Chaudhary *et al.* is so different from that of the claimed invention (page 6). See Applicants' amendment, pages 5-8. Applicants' arguments have been fully considered, but not found persuasive.

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Moreover, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, the use of fusion proteins to selectively target the delivery of nucleic acid molecules to a was known. Further, while the Examiner would agree that many types of ligands were used in targeting, it was readily known in the art that the use of an antibody provided the most specific and versatile targeting of any antigen. Thus, the reduction of practice of with one kind of ligand and the suggestion to use an antibody as another type of targeting ligand would readily be recognized in the art for providing the necessary teaching to successfully use an antibody to target an antigen of choice. As noted in the previous office action, Wu *et al.* specifically teach that an antibody provides an effective means for specifically targeting a fusion protein to a particular epitope on the surface of a desired cell (page 3, lines 7-11), and Chaudhary *et al.* teach that fusion proteins comprising antibodies and a second protein capable of targeting a desired cell were generated by conventional methods know and used at the time of filing (see example in figure 1). Additionally, Chaudhary *et al.* was cited for teaching that fusion proteins comprising antibodies can be generated by conventional methods know and used at the time of filing. Applicants' arguments that a ligand, not an antibody is taught in the combined references is not persuasive because both Wu *et al.* and Chaudhary *et al.* specifically provide the necessary teaching for the use of an antibody in the context of a fusion protein to target cell surface receptors on a desired cell. Examiner does note that Wu *et al.* teaches the use of chemical linkages however it was previously noted that Beug *et al.* specifically teach noncovalent means to bind a nucleic acid for example a ligand to polylysine, and that recombinant methods can be used to generate the recombinant protein (page 7). The teaching of Wu *et al.* relied upon by Applicants for teaching away does not teach away from the instantly claimed invention (column 5, lines 37-48), in fact it provides the basis for generating a recombinantly generated fusion

protein over one that is chemically linked. The portion pointed to by Applicants details how the polylysine can be linked to the ligand, however this has no effect on the ability of the polylysine to bind, deliver or release the nucleic acid in a cell.

With respect to unexpected results, contrary to Applicants assertion, Li does not provide a direct comparison of chemically linked versus recombinant forms, rather it is a comparison of different compositions made through the addition of the components in a different order. Li does not teach any chemical linkage, unless one were to include the non-covalent interactions of the components which the instantly claimed invention also requires, i.e. the interaction of the DNA binding domain with the nucleic acid. As noted in the previous office action, Applicants arguments that the present invention provides an improved selectivity which was not suggested in the art is unpersuasive because the focus of each Beug *et al.*, Chaudhary *et al.* and Wu *et al.* was to provide the targeted delivery of a complex to a cell of interest. In particular, Wu *et al.* demonstrates that providing a targeting moiety in the complex greatly increases the uptake to a cell. Further, the uptake is selective as demonstrated by comparing two human hepatoma cell lines one which contains the cell surface target, HepG2, and one which does not, SHKHep 1 (see figure 1). Chaudhary *et al.* demonstrate the selectivity of a fusion protein complex can range in the exponential scale as demonstrated by uptake and cytotoxicity in OVCAR3 cells (figure 5) or other related cell lines (Table 2). Any improved selectivity (as relied upon in the Li *et al.* reference) would be considered analogous to that provided by Chaudhary *et al.* and Wu *et al.* comparing cells which have or do not have the targeted cell surface ligand. Additionally, it is noted that in this portion of the Li *et al.* reference the discussion does not focus on the increased selectivity of the complexes, rather 'that the nonviral gene transfer systems reported here

disclosed require substantial improvement' (page 564, first full paragraph). Applicants' arguments are not persuasive because at the time of filing the focus of targeted complexes was to increase the uptake of the complex in the target cell. As generally expected, and as demonstrated by Chaudhary *et al.* and Wu *et al.*, recombinant proteins with a targeting moiety are more selectively taken-up by cells which contain the desired target.

Thus, at the time of filing Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching for all the embodiments encompassed by the instant claims, and the specific motivation to generate a recombinant targeting protein complex. In particular, where two protein components are provided, such as an antibody coupled to a second protein moiety, there is specific motivation to make this fusion protein recombinantly for the reasons set forth by Wu *et al.* and Chaudhary *et al.* Further, the use of a targeting antibody would generally be accepted to provide a more selective targeting, and as evidenced by Chaudhary *et al.* and Wu *et al.* the selection can be very great.

Therefore, for the reasons above and of record, the rejection is maintained.

Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as applied to claims 1, 3-5, 7-16 above, and in further view of Ryder *et al.* for the reasons below and as set forth in the previous office action.

Applicants argue that the teaching of Ryder *et al.* does not overcome the essential deficiency of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as discussed for claims 1, 3-5, 7-16. See Applicants' amendment, pages 8-9. Applicants' arguments have been fully considered, but not found persuasive.

As reasoned above, Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching and motivation to make obvious claims 1, 3-5, 7-16. Beug *et al.* and Wu *et al.* teach that any variety of polynucleotide binding sequences can be used in forming the complexes and attached to the targeting moiety, however specific polynucleotide sequences are not taught. Ryder *et al.* is relied upon to teach that at the time of filing among the various species of sequences recited in claim 6, the Jun DNA binding sequences were known. As noted in the previous office action, Ryder *et al.* is not relied upon to correct deficiencies of Beug *et al.*, Chaudhary *et al.* and Wu *et al.*, rather the teachings are relied upon to teach what was known in the art at the time of filing. Ryder *et al.* provide a detailed teaching for the specific DNA binding sequences and demonstrate that they are effective in binding target DNA as evidenced by the gel shift assay (see results in figure). Applicants' arguments are unpersuasive because Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching to make obvious claims 1, 3-5, 7-16, and claim 6 is obvious in light of the teaching of Ryder *et al.* for the specific c-jun DNA binding sequences.

Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach